

Claim 9, line 1, before "glycol", insert --polyoxyethylene--
polyoxypropylene--

REMARKS

Reconsideration of this application is requested in view of the amendments to the specification and claims and the remarks presented herein.

The claims in the application are claims 1 to 11, no other claims having been presented. The specification has now been amended to make reference to the PCT application.

Claims 1 to 11 were rejected under 35 USC 112, second paragraph, as being indefinite in the use of the terms "material" and "agent". Claims 3 and 9 were rejected as lacking antecedent basis for the terms therein and claims 1 and 6 were deemed to be duplicates of each other.

Applicants respectfully traverse these grounds of rejection since the amended claims properly define the invention. Claim 6 has been cancelled and the term "material" has been amended to recite the aqueous solution as kindly suggested by the Examiner. The same is true with respect to the term "agent". Therefore, there is now proper antecedent basis for claims 3 and 9. The amended claims comply with 35 USC 112 and withdrawal of this ground

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of rejection is requested.

All of the claims were rejected under 35 USC 103 as being obvious over the Ron reference taken in view of the conventional knowledge as set forth in the Condensed Chemical Dictionary. The Examiner states that the Ron reference teaches pharmaceutical formulations of osteogenic proteins comprising an osteogenic protein-sequestering material as set forth in the Abstract and the sequestering material useful are deemed in lines 17 to 26 of page 8 to include polyethylene glycol or polyoxyethylene oxide. The Examiner concedes that the reference does not teach the use of polyoxyethylene-polyoxypropylene glycol in the formulations. The Examiner cites the Chemical Dictionary as showing that Pluronic are non-ionic sequestering compounds which can be used in various compositions as dispersing agents for stabilizing and indicates that the Dictionary also refers to sequestration compounds and deems it would have been obvious to use the Pluronic for its sequestering properties and expect to obtain osteogenic protein formulation.

Applicants respectfully traverse this ground of rejection and the combination of the prior art, cited by the Examiner with the benefit of Applicants' disclosure, would not teach one skilled in the art Applicants' cartilage and bone morphogenetic repairing aqueous solutions as claimed. Applicants will agree with the Examiner's assertion that lines 17 to 26 of page 8 of the Ron

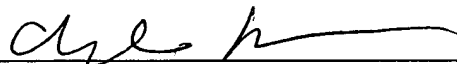
reference discloses that various sequestering agents include polyethylene glycol and polyoxyethylene oxide as being useful as an osteogenic protein sequestering material and not a sequestering material generally but, rather, mainly that a protein is the object of the sequestration. The Chemical Dictionary cited by the Examiner for the definition of Pluronics does not describe them as a sequestering compound but merely as a nonionic polymer as can be seen from page 891. The nonionic structure does not permit one to be led to the properties of "sequestration" as stated by the Examiner.

The "Pluronic polyol" is cited for example in the poly(oxyethylene-co-oxypropylene) nonionic surfactant which have functional properties which are well known as can be seen from the Encyclopedia of Chemical Technology, 3rd Edition, ppgs. 332, 333, 360, 376 and 377, copies of which are submitted herewith for the Examiner's convenience. The use of polyethylene glycol or polyethylene oxide described by Ron and the teaching of the Chemical Dictionary cited by the Examiner would not lead one skilled in the art to use Pluronics of an entirely different nature, namely, polyoxyethylene-polyoxypropylene glycol for its sequestering products since these are not evident to one skilled in the art and would not be formulated by one skilled in the art without the benefit of Applicants' teaching. Therefore, the combination of the prior art would not teach Applicants' invention and withdrawal of this ground of rejection is requested.

Page 8 of the application has been amended to correct the typographical error in reference to the application referred to in line 1.

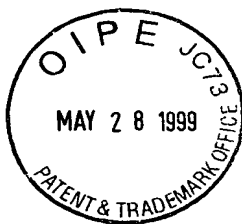
In view of the amendments to the specification and claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
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SUPERCRITICAL FLUIDS. See Supplement volume.

SUPEROXIDES. See Peroxides and peroxy compounds.

SUPERPHOSPHATE. See Fertilizers.

SURFACTANTS AND DETERGENT SYSTEMS

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SURFACTANTS

The term surfactant is a contraction of the longer, more awkward term surface-active agent. Coined in 1950, surfactant has become universally accepted to describe organic substances with certain characteristic features in structure and properties. The term detergent is often used interchangeably with surfactant. As a designation for a substance capable of cleaning, detergent can also encompass inorganic substances when these do in fact perform a cleaning chore. More often, detergent refers to a combination of surfactants with other substances, organic or inorganic, formulated to enhance functional performance, specifically cleaning, over that of the surfactant alone. It is so used in this article.

Surfactants are characterized by the following features:

Amphipathic structure. Surfactant molecules are composed of groups of opposing solubility tendencies, typically an oil-soluble hydrocarbon chain and a water-soluble ionic group.

Solubility. A surfactant is soluble in at least one phase of a liquid system.

Adsorption at interfaces. At equilibrium, the concentration of a surfactant solute at a phase interface is greater than its concentration in the bulk of the solution.

Orientation at interfaces. Surfactant molecules and ions form oriented monolayers at phase interfaces.

Micelle formation. Surfactants form aggregates of molecules or ions called micelles when the concentration of the surfactant solute in the bulk of the solution exceeds a limiting value, the so-called critical micelle concentration (CMC), which is a fundamental characteristic of each solute-solvent system.

Functional properties. Surfactant solutions exhibit combinations of cleaning (detergency), foaming, wetting, emulsifying, solubilizing, and dispersing properties.

The presence of two structurally dissimilar groups within a single molecule is the most fundamental characteristic of surfactants. The surface behavior, ie, the surface activity, of the surfactant molecule is determined by the make-up of the individual groups, their solubility properties, their relative size and their location within the surfactant molecule. The term amphipathy was proposed as "the occurrence in a single molecule or ion, with a suitable degree of separation, of one or more groups which have affinity (sympathy) for the phase in which the molecule or ion is dissolved, together with one or more groups which are antipathic to the medium (ie, which tend to be expelled by it)" (1).

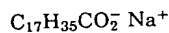
Different designations describe the opposing groups within the surfactant molecules, eg, hydrophobic, water hating and hydrophilic, water liking; lipophobic, fat hating and lipophilic, fat liking; oleophobic, fat (oil) hating and oleophilic, fat (oil) liking; lyophobic, solvent hating and lyophilic, solvent liking. The terms polar and nonpolar are also used to designate water-soluble and water-insoluble groups, respectively.

Hundreds of thousands of amphipathic combinations are theoretically possible. Thousands have been described in the literature covering most of the commercially important or theoretically interesting structures.

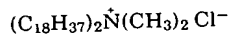
Surface activity is not limited to aqueous systems. All of the combinations of aqueous and nonaqueous phases are known to occur. However, because water is present as the solvent phase in the overwhelming proportion of commercially important surfactant systems, its presence is assumed in much of the common terminology of industry. Thus, the water-soluble amphipathic groups are often referred to as solubilizing groups.

Until the end of the 19th century, soap (qv), the alkali metal salt of long-chain carboxylic acids, was the only man-made surfactant. With the spread of chemical technology, particularly in the early years of this century, the technical shortcomings of soap, ie, its instability toward water hardness and acidity, were felt particularly acutely in the textile industry. Sulfonated oils were developed as hardness- and acid-stable dyeing and wetting assistants. A critical shortage of soap in Germany during World War I provided further incentive for the development of substitutes for the fat-derived hydrophobe. Further activity in Germany in the years following World War I led to many hundreds of new surfactant structures. These developments can be viewed as the beginning of the modern surfactant industry. The growth of the petrochemical industry after World War II further aided the growth of the surfactant industry in providing high quality, relatively inexpensive starting materials. During the last decade, however, the escalating cost of crude oil and simultaneous improvements in the production of oil-bearing seeds have led to a reexamination of oleochemical feedstocks as potential sources for surfactant manufacture. An extensive shift to oleochemicals is not likely, although some moves in this direction are in evidence.

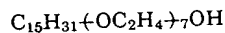
Surfactants are classified depending on the charge of the surface-active moiety, usually the larger part of the molecule. In anionic surfactants, this moiety carries a negative charge, as in soap:



In cationic surfactants, the charge is positive:



In nonionic surfactants, as the name implies, there is no charge on the molecule; the solubilizing contribution is supplied by a chain of ethylene oxide groups:



Finally, in amphoteric surfactants, solubilization is provided by the presence of positive and negative charges in the molecule, as in



In general, the hydrophobic group consists of a hydrocarbon chain containing ca 10–20

find application as specialty surfactants in situations where such limitations are of no concern. As specialty surfactants, phosphate esters and their salts are remarkably versatile. Applications include emulsion polymerization of vinyl acetate and acrylates; dry-cleaning compositions where solubility in hydrocarbon solvents is a particular advantage; textile mill processing where stability and emulsifying power for oil and wax under highly alkaline conditions is called for; and industrial cleaning compositions where tolerance for high concentrations of electrolyte and alkalinity is required. In addition, phosphate surfactants are used as corrosion inhibitors, in pesticide formulations, in papermaking, and as wetting and dispersing agents in drilling mud fluids.

Polyphosphoric acid, P_2O_5 , $POCl_3$, and PCl_3 are suitable phosphorylating agents. Reaction of an alkyl sulfate with sodium pyrophosphate has also been reported for preparation of alkyl pyrophosphates (69). In general, phosphorylation leads to a mixture of reaction products that are sold without further separation. Thus, when lauryltri(ethyleneoxy)ethanol reacts with $\frac{1}{3}$ mol of P_2O_5 at $50^\circ C$ and is neutralized with 50% aqueous NaOH, the reaction mixture contains the following products:

$C_{12}H_{25}[\text{OCH}_2\text{CH}_2]_4\text{OPO(OH)ONa}$ [82679-95-6]	monoester, largest fraction
$(C_{12}H_{25}[\text{OCH}_2\text{CH}_2]_4\text{O})_2\text{PO(ONa)}$ [28505-90-0]	diester, second largest fraction
$(C_{12}H_{25}[\text{OCH}_2\text{CH}_2]_4\text{O})_3\text{PO}$ [20297-06-7]	triester, small fraction

and smaller amounts of the phosphate esters of the polyethylene glycol which is present in the ethoxylated alcohol. A trace of NaH_2PO_3 is also present.

Table 14 gives the important commercial phosphate surfactants which are offered commercially under a variety of trade names including Crodafos, Emphos, Findet, Gafac, Hodag PE, Hostaphat, Monafax, Rexophos, Triton, Victawet, and others.

Nonionic Surfactants

Unlike anionic or cationic surfactants, nonionic surfactants carry no discrete charge when dissolved in aqueous media. Hydrophilicity in nonionic surfactants is provided by hydrogen bonding with water molecules (71). Oxygen atoms and hydroxyl groups readily form strong hydrogen bonds, whereas ester and amide groups form hydrogen bonds less readily. Hydrogen bonding provides solubilization in neutral and alkaline media. In a strongly acid environment, oxygen atoms are protonated, providing a quasi-cationic character. Each oxygen atom makes a small contribution to water solubility. More than a single oxygen atom is therefore needed to solubilize a nonionic surfactant in water. Nonionic surfactants are compatible with ionic and amphoteric surfactants. Since a polyoxyethylene group can easily be introduced by reaction of ethylene oxide with any organic molecule containing an active hydrogen atom, a wide variety of structures can be solubilized by ethoxylation.

Polyoxyethylene Surfactants (Ethoxylates). Polyoxyethylene-solubilized nonionics were introduced in the United States as textile chemicals shortly before 1940. The solubility of these compounds derives from recurring ether linkages in a polyoxyethylene chain $-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-$. A single oxyethylene group, $-\text{OCH}_2\text{CH}_2-$ contributes slightly more to hydrophilicity than a single methylene, CH_2 , contributes to hydrophobicity. To effect complete miscibility with water at room temperature, ca 60–75% by weight of polyoxyethylene content is needed on most hydrophobes. With increasing temperature, ethoxylates become less soluble as a result of decreased hydration and increasing micellar size (72–73). The temper-

Table 25. Monoalkanolamides of Fatty Acids

Trade name	Fatty acid	Amine	Concn, wt %	Functions ^a	Manufacturer ^b
Ardet LIPA	lauric	isopropanol	93	Fs	ARD
Cerasynt D	stearic	ethanol	100	E, O, V	VND
Clindrol 101LI	lauric	isopropanol	100	D, Fs	CLI
Emid 6500	coco	ethanol	100	Fs, V	EMR
Intermediate 300	tallow/coco	ethanol	100	Fs, St, V	HUM
Intermediate 325	coco	ethanol	100	Fs, St, V	HUM
Monamid LIPA	lauric	isopropanol	100	Fs, V	MOA
Monamid LMA	lauric	ethanol	100	Fs, V	MOA
Monamid S	stearic	ethanol	100	O	MOA
P&G Amide No. 27	coco	ethanol	100	Fs, St, V	PG
Schercomid CME	coco	ethanol	100	D, Fs	SBC
Schercomid SME	stearic	isopropanol	100	D, E, O, V	SBC
Sole-Onic MIO	oleic	isopropanol	100	A, H	HDG
Surco CMEA	coco	ethanol	100	Fs, O, V	OXR
Witcamide 61	oleic	isopropanol	>90	C, E, V	WTC
Witcamide 70	stearic	ethanol	>90	C, O, V	WTC
Witcamide MM	myristic	ethanol	>90	C, O, V	WTC

^a See Table 1.^b See Table 2.

chain ethylene oxide adducts of fatty amides sometimes exhibit special properties. Some representative products are given in Table 26.

Polyalkylene Oxide Block Copolymers. The higher alkylene oxides derived from propylene, butylene, styrene, and cyclohexene react with active oxygens in a manner analogous to the reaction of ethylene oxide. Because the hydrophilic oxygen constitutes a smaller proportion of these molecules, the net effect is that the oxides, unlike ethylene oxide, are hydrophobic. The higher oxides are not used commercially as surfactant raw materials except for minor quantities that are employed as chain terminators in polyoxyethylene surfactants to lower their foaming tendency. The hydrophobic nature of propylene oxide units, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{O}-$, has been utilized in several ways in the manufacture of surfactants. Manufacture, properties, and uses of poly(oxyethylene-co-oxypropylene) are reviewed in ref. 83.

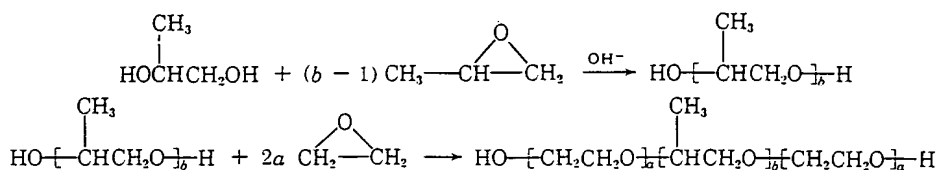
Poly(oxyethylene-co-oxypropylene) Nonionic Surfactants. A great variety of these products is marketed by the BASF Wyandotte Corp under the Pluronic polyol

Table 26. Polyoxyethylene Fatty Acid Amides

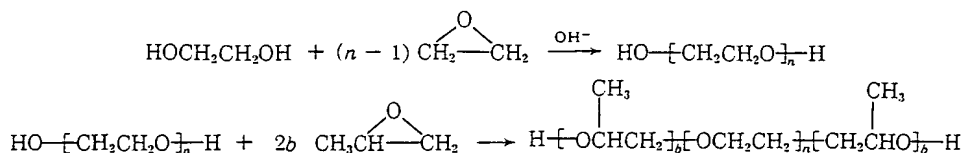
Trade name	Fatty acid	POE ^a	Concn, wt %	Functions ^b	Manufacturer ^c
Amidox C-2	coco	2	100	D, E, Fs	STP
Amidox C-5	coco	5	100	D, E, Fs	STP
Amidox L-2	lauric	2	100	D, E, Fs	STP
Amidox L-5	lauric	5	100	D, E, Fs	STP
Ethomid HT/15	hydrogenated tallow	5	100	D, Di, E	AMK
Ethomid HT/60	hydrogenated tallow	50	100	D, Di, E	AMK
Ethomid O/17	oleic	5	100	D, Di, E	AMK

^a No. of ethylene oxide groups in polyoxyethylene.^b See Table 1.^c See Table 2.

trademark. The synthesis is shown below:



The structure of individual block polymers is determined by the nature of the initiator (1,2-propanediol in the above example), the sequence of addition of propylene and ethylene oxides, and the percentage of propylene and ethylene oxides in the surfactant. Thus, when the order of addition is reversed, a different structure is obtained in which the hydrophobic moieties are on the outside of the molecule. With ethylene glycol as the initiator, the reactions are as follows:



A third series of surfactants can be prepared by simultaneous addition of ethylene oxide and propylene oxide. Initially, propylene oxide predominates in the mixed oxides. In the second reaction step, ethylene oxide predominates. With a trifunctional initiator, eg, 1,1,1-trimethylolpropane, the final surfactant structure consists of three polyoxyalkylene chains each containing blocks of polyoxyethylene and polyoxypropylene, attached to a single carbon (84). Pluronic polyol surfactants vary from mobile liquids to flakeable solids. Solubility in water ranges from slightly soluble to completely miscible at the boil. Pluronic polyols with high ethylene oxide content exhibit no solution cloud point even at 100°C. In general, they are soluble in aromatic solvents but insoluble in kerosene or mineral oil. They exhibit very low toxicity and are nonirritating to the skin and almost tasteless. Chemical stability is comparable to that of the alcohol ethoxylates.

Block polymer nonionic surfactants are not strongly surface active but exhibit commercially useful surfactant properties. Aqueous solutions characteristically foam less than those of other surfactant types. They act as detergents, wetting and rinsing agents, demulsifiers and emulsifiers, dispersants and solubilizers. They are used in automatic dishwashing-detergent compositions, cosmetic preparations, spin finishing compositions for textile processing, metal-cleaning formulations, papermaking, and other technologies.

Block polymer nonionic surfactants are also manufactured by Dow Chemical Co., Union Carbide, and Witco Chemical Corp.

Cationic Surfactants

As the name implies, the hydrophobic moiety of a cationic surfactant carries a positive charge when dissolved in aqueous media. The positive charge resides on an amino or quaternary nitrogen. A single amino nitrogen is sufficiently hydrophilic to solubilize a detergent-range hydrophobe in dilute acidic solution; eg, laurylamine is soluble in dilute hydrochloric acid. For increased water solubility, additional primary, secondary, or tertiary amino groups can be introduced or the amino nitrogen can be